

APPLICATION OF AN ELECTRO-CHEMICAL PROCEDURE TO THE PRODUCTION OF ^{18}F -PHARMACEUTICALS

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Abstract

^{18}F in enriched [^{18}O]-water was electro-deposited on a graphite electrode and then electro-emitted into aprotic polar solvent, acetonitrile. In a previous work [1], the fraction of the electro-deposited ^{18}F was 97%. In the present work, however, the fraction decreased to 24%. The descent is attributed to considerably high concentration of contaminants in [^{18}O]-water from the ion bombardment of a silver target. The fraction of the electro-emitted ^{18}F into acetonitrile was sufficiently high. This result indicates that ^{18}F ions solvated with solvent molecules and remained stable in an aprotic polar solvent. Thus, the electrochemical method can effectively transfer high purity ^{18}F ions from enriched [^{18}O]-water to a high purity polar solvent. We expect to develop simple and effective syntheses of diverse ^{18}F -radiopharmaceuticals using the electrochemical method.

INTRODUCTION

Positron Emission Tomography (PET) is capable of highly precise diagnosis of tumours. The increasing demand for PET are promoting building large scale PET facilities and organizing delivery networks of radiopharmaceuticals. ^{18}F -labelled compounds are most widely used radiopharmaceuticals, since half-life of ^{18}F (110 min.) is long enough to synthesize labelled compounds and to use those for routine clinical purposes. ^{18}F is usually produced via the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction on enriched [^{18}O]-water bombarded by protons. This method produces a large amount of activity and provides carrier-free ^{18}F ions.

The produced ^{18}F ions are separated from the [^{18}O]-water in order to proceed with the nucleophilic reactions and recover the [^{18}O]-water. The separation is performed by trapping ^{18}F on an ion exchange resin and flushing the [^{18}O]-water. The trapped ^{18}F is eluted into the mixture of acetonitrile and water containing $\text{K}^+/\text{Kryptofix 2.2.2}$. The

water is removed by azeotropic evaporation before synthesis. This method results in high efficiency of recovery of ^{18}F and is convenient for an automated apparatus. Most widely used ^{18}F -labelled compound, [^{18}F]fluoro-2-deoxy glucose ([^{18}F]FDG) is produced using this method for clinical purposes. The reuse of [^{18}O]-water is, however, limited to 3-5 times, since the concentration of ^{16}O -water and organic compounds in [^{18}O]-water increases. The increase in the concentration brings about the rising of target pressure to break the target foil during irradiation. Furthermore, it is said radiochemical yields decreases seriously due to metal contaminants from the target. For diagnostic use in facilities, stable and effective production of the ^{18}F -labelled compounds is crucially important [2].

Ideally, ^{18}F should be transferred into solvents without any contaminants. Electro-chemical method is expected to transfer high purity ^{18}F to high purity solvents [1]. The method consists of three processes; the first is electro-deposition of ^{18}F . ^{18}F ions in [^{18}O]-water are electro-deposited on a graphite anode and residual [^{18}O]-water is recovered without any additives. The second is electro-emission of ^{18}F . The ^{18}F ions deposited on the graphite electrode are emitted into a solvent with inversed electric polarity. The third is ^{18}F -labelling of substrates. It may be possible to perform the second and the third process simultaneously, using a solution containing a substrate.

In the present work, we report the experiments of the first and the second process and discuss the possibility of the third process.

EXPERIMENTALS

Anhydrous acetonitrile (99.8%) was purchased from Sigma-Aldrich and used without further purification. Enriched [^{18}O]-water obtained from Sceti Company (97.5%) and Rotem Industries (95%) was used without distillation.

The [^{18}F] fluoride was produced using a cyclotron (IBA) in the Department of Radiology, Yokohama City

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University Hospital. About 2ml of enriched [^{18}O]-water in a silver target with a Haver foil window was irradiated by 18MeV protons of 30 μA . The activity of the ^{18}F produced was 170-940mCi after the irradiation for 7-40 minutes.

The irradiated [^{18}O]-water was transferred through a Teflon tube to the apparatus for electro-deposition and electro-emission placed in a hot cell. The details of the apparatus are given elsewhere [1]. Three syringe pumps were added to the apparatus to recover [^{18}O]-water and to supply and recover acetonitrile. The electrochemical apparatus and syringe pumps were operated by PC aided controls.

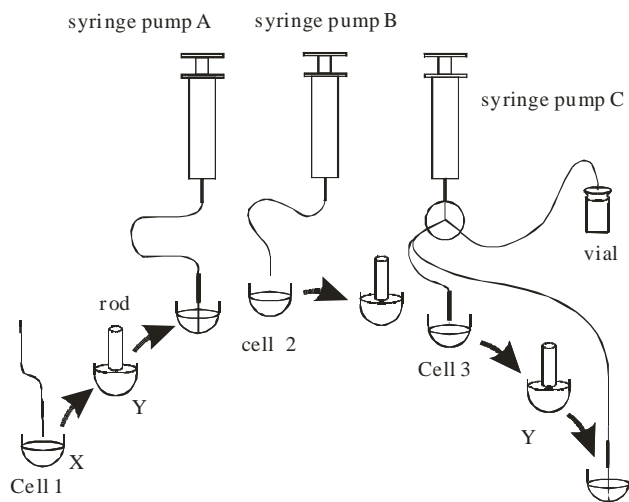


Figure 1: Diagram of apparatus

Figure 1 shows the experimental process. After a platinum cell 1 on a turning table was filled with the irradiated [^{18}O]-water at position X, the table turned so that the cell were located to position Y below a graphite rod. Graphite rods were purchased from Nilaco Co. and treated in the same way as the previous work [1]. The graphite rod was fixed on the side of a turning disc which moved up and down. For electro-deposition, the turning disc was lowered so that the end of the graphite rod was 1mm below the surface of the water. The surface was detected by monitoring the electric current which began to flow at the moment the graphite rod touched the surface. ^{18}F ions were electro-deposited on the graphite rod anode to which the voltage 200-300V was applied for 5-10min. Following the electro-deposition, the irradiated [^{18}O]-water was eluted from the cell 1 using a syringe pump A. Acetonitrile (2ml) was supplied in a platinum cell 2 by a syringe pump B for rinsing adsorbed water from the graphite rod surface. The graphite rod was dipped into the acetonitrile for 1 minute. Then, the turning disc was raised and turned to make the graphite rod face to the end of a tube where the rod was dried with a blow of nitrogen gas.

The deposited ^{18}F was then recovered electrically into high purity acetonitrile. A syringe pump C with a 3-way valve supplied acetonitrile (2ml) to a platinum cell 3.

After the cell 3 was carried to the position Y, the turning disc was turned and lowered so that the end of the graphite rod was located 2mm below the surface. The deposited ^{18}F was emitted into the acetonitrile in the cell 3 (anode) by applying the voltage of 200-600V for 5-15min. The voltage and the electric current were recorded during the period of electro-depositing and electro-emitting. The ^{18}F solution was eluted into a vial using the syringe pump C.

After the series of electrochemical operations, the platinum cells and the electrodes were dismantled of the apparatus in order to know their activities. The activities of the platinum cells, the graphite electrodes, the recovered [^{18}O]-water, the rinsing acetonitrile and the ^{18}F solution were measured using a dose calibrator to obtain the fractions of the electro-deposited ^{18}F and the electro-emitted ^{18}F . γ ray energy spectra of these samples were also measured 2 days after the electro-chemical operations.

RESULTS AND DISCUSSION

In the previous work [1], almost all ^{18}F in the water was electrodeposited on a graphite rod. The fractions of electro-deposition i. e., the ratio of the activity of the ^{18}F deposited to that of the total amount of the ^{18}F for the present work (24%), were considerably lower than that for the previous work (97%). The activity of the ^{18}F deposited was the sum of the activities of the graphite rod, the rinsing platinum cell 2, the rinsing acetonitrile, the emission cell 3 and recovered ^{18}F solution. The activity of the total amount of the ^{18}F was the sum of the activities of the cell 1, the recovered [^{18}O]-water and those mentioned. The low fraction seemed to be ascribed to impurities contained in the irradiated [^{18}O]-water. The high concentration of impurities, especially Ag, is resulted from using a silver target [3]. In the previous work, a titanium target was used.

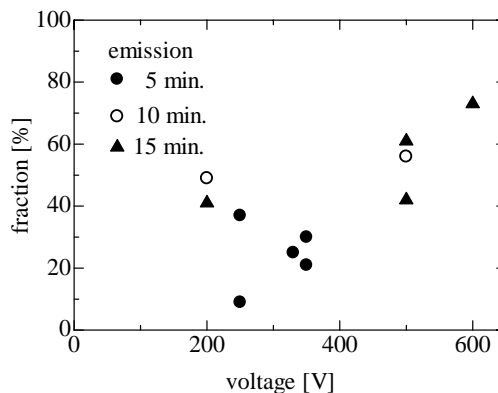


Figure 2: Dependence of the fractions of electro-emission on applied voltages

In the previous work [1], we reported efficient recovery of ^{18}F in ultra-pure water using the electrochemical method. In the present work, ^{18}F was recovered in aprotic polar solvent, acetonitrile. The fraction of recovery by electro-emission was defined as the ratio of the activity of the emitted ^{18}F into acetonitrile to that of the ^{18}F deposited on the graphite electrode. Figure 2 shows the fractions of electro-emission. We see the tendency that longer electro-emission time and higher voltage caused higher fractions. The highest fraction was 73% with the electro-emission for 15 minutes. The results indicate that the electro-emission is an effective method to transfer $^{18}\text{F}^-$ ions into polar solvent. The $^{18}\text{F}^-$ ions in acetonitrile seems to be solvated with solvent molecules as well as in water. Thus, $^{18}\text{F}^-$ ions remain stable in an aprotic polar solvent without K^+ /Kryptofix 2.2.2.

Metal RI cation impurities produced by the irradiation of the target were efficiently removed by electrochemical method [1]. In the present work, this effect was confirmed with acetonitrile with high concentration of impurities. Figure 3 shows γ ray energy spectra of the recovered ^{18}O water, a graphite electrode and the recovered ^{18}F solution. We see several peaks from RI impurities in addition to the annihilation γ (511keV). Furthermore, we notice that most of the RI impurities were contained in the recovered ^{18}O water. Though some impurities were adsorbed on the graphite anode, they were hardly emitted into acetonitrile; the activities of the impurities in the acetonitrile were nearly background level.

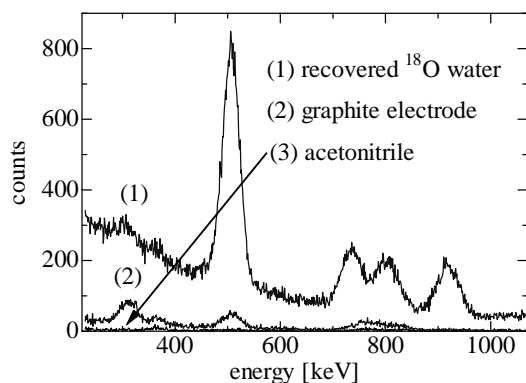


Figure 3: γ ray spectra of (1) recovered ^{18}O water, (2) graphite anode and recovered ^{18}F solution

The electrochemical method makes it possible to transfer high purity ^{18}F ions from ^{18}O -water to high purity polar solvents. Thus, high purity and neutron-free simple chemical compounds, such as $^{18}\text{F}^-$ NaF is easily produced using this method. Furthermore, we expect to synthesize ^{18}F -pharmaceuticals in high purity aprotic polar solution. The synthesis of radiopharmaceuticals in high purity solution produces a high radiochemical yield.

We may also get rid of the use of potassium and phase transfer catalyst (Kryptofix 2.2.2). Potassium and Kryptofix 2.2.2 are believed to interfere with the substitution of ^{18}F and affect radiochemical yields. Moreover, Kryptofix 2.2.2 is deadly poisonous for a human body. We also expect to produce ^{18}F -labelled compounds in a short time using the electrochemical method, since this method dispenses with evaporations to remove water and Kryptofix 2.2.2. The evaporations take a rather long time in an automated process of synthesizing labelled compounds. If some reagents or catalysts are required, such chemicals are simply to be added in the high purity solution before or after the transferring of the $^{18}\text{F}^-$ ions. Rather high voltage applied for electro-emission may also promote the reaction.

In conclusion, electrochemical method can effectively transfer high purity ^{18}F ions from enriched ^{18}O -water to high purity polar solvent. We expect to develop a new automated system to synthesize ^{18}F -pharmaceuticals based on the electrochemical method.

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